REMARKS

Response to rejection of claims 11-14, 17, and 19 under 35 U.S.C. § 103 based on Tanaka in view of Broten in light of the Mesh Supplementary Data

Claims 11-14, 17, and 19 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tanaka et al. (WO 00/02846) (hereinafter "Tanaka") in view of Broten et al. (U.S. Patent No. 6,410,554) (hereinafter "Broten") in light of the Mesh Supplementary Data (2009). Applicants respectfully traverse on the basis that (1) the teachings of Tanaka and Broten do not provide a reason to a person having ordinary skill in the art to use silodosin alone or in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence; and (2) the unexpected results obtained by the presently claimed invention rebut any *prima facie* case of obviousness that may have been set forth.

(1) The teachings of Tanaka and Broten do not provide a reason to a person having ordinary skill in the art to use silodosin alone or in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence. As the Office Action has admitted, Broten only teaches the administration of KMD-3213 (actually, in combination with an endothelin antagonist - not alone) for the treatment of lower urinary tract symptoms including increasing urine flow rate, decreasing residual urine volume and improving overall obstructive and irritative symptoms in patients with benign prostatic hyperplasia (see column 6), and that KMD-3213 can be administered at a dosage from 0.01 to 500 mg per subject (see column 13). In this connection, Broten specifically teaches that an α1-a antagonist will inhibit the intraurethral pressure response to phenylephrine (see Example 14).

However, Broten does not teach or suggest the effect of ENID-3213 on frequency or urinary incontinence.

As Broten also teaches, α1A-adrenoceptor antagonists may inhibit prostatic urethral contraction (see column 30, Example 14). On the other hand, α1-adrenoceptor agonists induce contraction of the urethra. Nishimatsu et al. (see the Abstract of the attached reference) teach that an α1-adrenoceptor agonist (NS-49) is considered useful for the treatment of urinary stress incontinence due to the effect of contraction of the human urethra. Therefore, one of ordinary skill in the art would not expect that silodosin, an α1A-adrenoceptor antagonist having the opposite activity, would be effective for the treatment of urinary incontinence.

In addition, for the treatment of frequency or urinary incontinence, anticholinergics, antispasmodics, and the like have been used (see the attached portion of American Family Physician, 2006, Vol. 74(12), 2061-2068), and β3 adrenoceptor agonists are developed (see, for example, Tanaka, column 2, lines 34-41 and column 3, lines 13-18). These drugs are targeted mainly to smooth muscle of the bladder (see the attached portion of American Family Physician, at p. 2061, left column, lines 1-6 and the paragraph entitled "Pathophysiology" at p. 2061, right column to p. 2063, left column, line 7). As of the filing date of the present application, however, there was no report showing that silodosin has an inhibitory activity against contraction of the bladder, whereas silodosin was known to suppress uretheral contraction and be useful as an agent for the treatment of dysuria (column 9, lines 37 and U.S. Patent No. 5,387,603 at column 1, lines 7-14). "Dysuria" means difficulty or pain in urination (see the attached definition from Stedman's Medical Dictionary). Therefore, a person having ordinary skill in the art would not have expected (with any reasonable expectation of success) that silodosin would be effective for the treatment of frequency or urinary incontinence.

Furthermore, in the micturition interval measurement as shown in Example 2 of the present specification, the inventors used the acetic acid-stimulated frequency model, which is a frequency model independent of the presence or absence of urinary obstruction. Therefore, the results on silodosin show the direct effect improving urinary frequency of silodosin, not a secondary effect by inhibiting contraction of urethra.

Accordingly, Applicants respectfully submit that the teachings of Tanaka and Broten do not provide a reason to a person having ordinary skill in the art to use silodosin alone or in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence.

(2) The unexpected results obtained by the presently claimed invention rebut any *prima facie* case of obviousness that may have been set forth. Although Applicants submit that, for at least the reasons set forth above, the Office Action failed to set forth a *prima facie* case of obviousness, Applicants respectfully submit that the unexpectedly superior results demonstrated in the present specification rebut any such showing.

Applicants first respectfully disagree with the position set forth in the Office Action that "in order for superadditive or superior results to be concluded, each agent must be administered at the same dosage and then the combination of the two agents compared to the change of micturition interval demonstrated by each individual agent." It is unclear what authority the Office is citing for such a position, and Applicants respectfully submit that such a position is incorrect.

As shown in Example 2 and Figure 2 of the present specification, the changes in the micturition intervals were 99.5%, 115.2%, 116.3% and 163.8% in the control group, the silodosin administration group, the compound 2 administration group, and the combination

group thereof, respectively. The differences of the change in micturition interval from control group are also shown in the following table.

Group	Control group	Silodosin group	Compound 2 group	Combination group
Dosage of Silodosin (mg/kg)	0	0.03	0	0.03
Dosage of Compound 2 (mg/kg)	0	0	1	1
Change in micturition interval	99.5	115.2	116.3	163.8
Difference from control group (%)	-	+15.7	+16.8	+64.3

The table illustrates that in the silodosin group, the micturition interval increased by 15.7% more than that in the control group, and in the Compound 2 group, it increased by 16.8% more than that in the control group. If the combination administration of silodosin and Compound 2 were to give only additive results, it would be expected to increase by only 32.5% (15.7% plus 16.8%) more than the control group. Unexpectedly, however, the combination administration exerted 64.3% more than control group, which is almost two times higher than expected.

Furthermore, it was also confirmed that the combined administration of silodosin and compound 2 exhibited a synergistic effect by a statistical method as well (see Paragraph No. [0030] of the present specification).

Accordingly, although Applicants disagree that the Office Action set forth a *prima facie* case of obviousness, Applicants respectfully submit that the unexpected results obtained by the presently claimed invention rebut any *prima facie* case of obviousness that may have been set forth.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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STEDMAN'S
Medical Dictionary

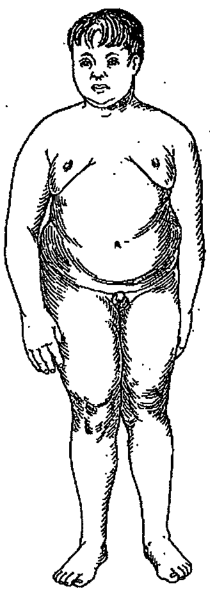
ILLUSTRATED / 23

and coming to lie in the corresponding half of the scrotum; see also *descensus* paradoxus testis.

dystop'ic. Malplaced; ectopic; out of place.

dystrophia (dis-tro'fĭ-ah) [L. fr. G. *dys-*, bad, + *trophē*, nourishment]. Dystrophy.

d. adiposogenita'lis, adiposogenital dystrophy; adiposogenital syndrome; hypophysis syndrome; adiposis orchica; an imperfectly understood and often misdiagnosed disorder. It is called Fröhlich's syndrome when caused by an adenohypophysial tumor; may also be caused by hypothalamic lesions in areas regulating appetite and gonadal development. It is characterized primarily by obesity and genital hypoplasia. Dwarfism is rare; when present, it is thought to reflect hypothyroidism.



Dystrophia Adiposogenitalis, Juvenile Type

(From Goldzieher, M. A.: *The Endocrine Glands*, Appleton-Century-Crofts, Inc., New York, 1939.)

d. brevicollis (brev-ĭ-kol'lis), a condition marked by symptoms of d. adiposogenitalis together with a deforming shortness of the neck, but without synostosis of the cervical vertebrae seen in Klippel-Feil syndrome.

d. endothelia'lis cor'neae, cornea guttata (Vogt); droplike corneal endothelial prominences.

d. epithelia'lis cor'neae, Fuchs' epithelial *dystrophy*.

d. myoton'ica, myotonic *dystrophy*.

d. un'guium, dystrophy of the nails.

dystrophic (dis-trof'ik). Relating to dystrophy.

dystrophoneurosis (dis-trof'o-nu-ro'sis) [dys- + G. *trophē*, nourishment, + *neuron*, nerve, + suffix *-osis*, condition]. Any nervous disease associated with faulty nutrition.

dystrophy (dis'tro-fĭ) [dys- + G. *trophē*, nourishment]. Dystrophia; defective nutrition.

adiposogenital d., *dystrophia* adiposogenitalis.

Barnes' d., a rare type of muscular d., with muscles often hypertrophic and stronger than normal early, but later becoming weak and atrophic.

childhood muscular d., a heritable disorder primarly afflicting boys. Between the ages of 2 and 6 years, muscular weakness first appears in the pelvic girdle and spreads with relative rapidity to the musculature of the pectoral girdle, trunk, and extremities; muscular pseudohypertrophy (enlarged, weakened, inelastic masses) is a common finding, as are contractures of muscle and tendon. Also called pseudohypertrophic d.; pseudomuscular hypertrophy; pseudohypertrophic muscular paralysis; Duchenne's d., disease, or paralysis.

craniocarpotarsal d., Freeman-Sheldon syndrome; whistling face syndrome; congenital association of skeletal defects (ulnar deviation of hands with camptodactyly, talipes equinovarus, and frontal bone defects) and characteristic facies (protrusion of lips as in whistling, sunken eyes with hypertelorism, and small nose); autosomal dominant inheritance.

Duchenne's d., childhood muscular d.

elastic d., elastic tissue degeneration as observed in chronic actinic effect, senile elastosis, etc.

facioscapulohumeral muscular d., Landouzy-Déjérine d.; a relatively benign type of d. commencing in childhood and characterized by wasting and weakness, mainly of the muscles of the face, shoulder girdle, and arms; autosomal dominant inheritance.

fleck d. of cornea, a bilateral condition characterized by the presence of subtle spots in the corneal stroma; the spots vary in size and shape, and have sharp margins and clear centers; photophobia or increased sensitivity may or may not be present; autosomal dominant inheritance.

Fuchs' epithelial dystrophy, dystrophia epithelialis corneae; a condition dependent on a prior endothelial d. of the cornea; it begins with a fine spreading central edema, is eventually bilateral, and occurs predominantly in elderly women.

Groenouw's corneal d., (1) a granular type, with autosomal dominant inheritance; (2) a macular type, with autosomal recessive inheritance.

gutter d. of cornea, keratoleptynsis; a marginal furrow usually inferiorly about 1 mm. from limbus and sometimes bilateral; an occasional complication of keratoconjunctivitis sicca and rheumatoid arthritis.

Landouzy-Déjérine d., facioscapulohumeral muscular d.

lattice corneal d., a reticular type of d. with autosomal dominant inheritance; it is manifest at puberty and progresses slowly; eventually useful vision is lost.

Leyden-Möbius muscular d., limb-girdle muscular d.

limb-girdle muscular d., Leyden-Möbius muscular d.; pelvofemoral muscular d.; a progressive disorder that usually begins in the preadolescent period; manifestations include those of childhood and facioscapulohumeral muscular d.; commonly, the pelvic girdle is most severely involved; autosomal recessive inheritance.

muscular d., myodystrophia; myodystrophy; inborn abnormality of muscle associated with dysfunction and ultimately with deterioration.

myotonic d., dystrophia myotonica; myotonia atropica or dystropica; Steinert's disease; a familial, chronic, and slowly progressive disease inherited as autosomal dominant, with onset usually in the third decade, and marked by atrophy of the muscles, failing vision, lenticular opacities, ptosis, slurred speech, and general muscular weakness; there may be atelectasis of the lungs and cyanosis due to involvement of the diaphragm.

pelvofemoral muscular d., limb-girdle muscular d.

progressive muscular d., Erb's atrophy; a form of progressive muscular atrophy in which the disease begins in the muscle and not in the spinal centers.

progressive tapetochoroidal d., choroideremia (2).

pseudohypertrophic muscular d., childhood muscular d.

Salzmann's nodular corneal d., large and prominent nodules of a solid, opaque material that stands out from the surface of the cornea. Occurs occasionally in persons previously affected by phlyctenular keratitis.

sympathetic reflex d., an illness consisting of superficial and deep pain of a spreading and burning character, vasomotor disturbances, trophic changes, and limitation of movement, occurring in an extremity after some physical disturbance in that extremity.

dystropy (dis'tro-pĭ) [dys- + G. *tropos*, a turning]. Abnormal or eccentric behavior.

dysuria (dis-u'rĭ-ah) [dys- + G. *ouron*, urine]. Difficulty or pain in urination.

dysuric (dis-u'rik). Relating to or suffering from dysuria.

dysury (dis'u-rĭ). Dysuria.

dysversion (dis-ver'zhun) [dys- + L. *verto*, to turn]. A turning in any direction, less than inversion; particularly d. of the optic nerve head (situs inversus of the optic desk).

Newer Agents for the Management of Overactive Bladder

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The anticholinergics tolterodine and oxybutynin are well established in the management of overactive bladder. However, their activity at muscarinic receptors distant from the target site (i.e., bladder) produces anticholinergic side effects leading to poor tolerability. In 2004, trospium, solifenacin, and darifenacin were approved by the U.S. Food and Drug Administration for the treatment of overactive bladder. Trospium is water soluble and therefore is less likely to enter the central nervous system, and solifenacin and darifenacin are more selective for the bladder than older agents. Although these attributes could improve tolerability, clinical trials comparing relevant agents to validate this are lacking. Trials have shown that these newer agents decrease the frequency of incontinence episodes, the number of voids per day, and the number and severity of urgency episodes compared with placebo. These agents also have been shown to improve quality of life in women with overactive bladder and urinary incontinence. Head-to-head studies of the newer agents and immediate-release oxybutynin and tolterodine have suggested similar effectiveness across the class, although the newer agents are better tolerated. Trospium and darifenacin have not been compared with extended-release formulations of tolterodine or oxybutynin, which are better tolerated than the immediate-release versions. In one study, solifenacin produced a somewhat greater decrease in the number of incontinence episodes than extended-release tolterodine, with no difference in tolerability. In general, the newer agents appear to be at least as effective as their predecessors, although it is unclear whether they are better tolerated. Important pharmacokinetic differences among the agents (e.g., route of elimination) allow for selection of an appropriate agent based on individual factors such as cost and tolerability. (Am Fam Physician 2006;74:2061-8. Copyright © 2006 American Academy of Family Physicians.)

Overactive bladder is a clinical syndrome characterized by one or more symptoms of urgency (a difficult-to-defer need to urinate), frequency (greater than eight urinations per 24 hours), nocturia, and incontinence. In persons without overactive bladder, the need to empty the bladder becomes progressively more demanding; in overactive bladder, urgency is characterized by unheralded messages of an immediate need to empty the bladder. These signals are difficult (and sometimes impossible) to delay. The inability to delay urination results in episodes of incontinence in up to 40 percent of patients with overactive bladder.

At present, the only class of drugs with widely accepted clinical effectiveness for the treatment of overactive bladder is the anticholinergics, typified by tolterodine (Detrol; Detrol LA) and oxybutynin (Ditropan; Ditropan XL). However, because these drugs create widespread blockade of cholinergic activity, they may cause anticholinergic adverse effects such as blurred vision, dry mouth, urinary retention, constipation, and central nervous system (CNS) effects such as somnolence and confusion. These effects are dose dependent but often occur at therapeutic doses. In 2004, three new anticholinergic drugs were approved by the U.S. Food and Drug Administration for the management of overactive bladder: trospium (Sanctura), solifenacin (Vesicare), and darifenacin (Enablex). *Table 1*[1-9] provides an overview of all five agents; key clinical trials of the newer agents are summarized in *Table 2*.[10-16]

Pathophysiology

Normally, during bladder filling the detrusor wall relaxes and the urethral sphincter contracts, promoting urine storage. During the normal voiding process, when threshold bladder volume has been reached, a decrease in urethral pressure and relaxation of the urethral sphincter precedes contraction of the detrusor muscle. At the same time, the pelvic floor muscles relax and the bladder neck forms a funnel. Parasympathetic stimulation of the detrusor muscle, mediated by

SORT: KEY RECOMMENDATIONS FOR PRACTICE		
Clinical recommendation	*Evidence rating*	*References*
Nonpharmacologic therapy is recommended for all patients with overactive bladder.	A	17-19
All available anticholinergic agents effectively decrease the frequency of urgency and incontinence episodes; one should be offered to patients who remain symptomatic despite nonpharmacologic therapy.	A	26, 31
Anticholinergics should be selected on the basis of cost and tolerability.	C	19, 22, 26, 31
Extended-release formulations of oxybutynin (Ditropan) and tolterodine (Detrol) are better tolerated than immediate-release versions.	A	23-31
The lowest effective dose of anticholinergics should be prescribed to avoid dose-dependent adverse effects.	C	26, 31

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 2008 or http://www.aafp.org/afpsort.xml.

TABLE 1
Overview of Anticholinergic Agents for Treatment of Overactive Bladder

Drug	*Availability*	*Dose*	*Frequency*	*Cost per month (generic)**	*Uroselective?*	*Route of elimination*
Darifenacin (Enablex)	ER tablet: 7.5, 15 mg	7.5 to 15 mg	Once daily without regard for meals	$96	Yes	Hepatic (CYP 3A4)
Oxybutynin (Ditropan; Ditropan XL)	IR tablet: 5 mg	2.5 to 5 mg	Two to four times daily	(13 to 30)	No	Hepatic (CYP 3A4)
	IR syrup: 5 mg per 5 mL	2.5 to 5 mg	Two to four times daily	75 to 113 (24 to 36)		
	ER tablet: 5, 10, 15 mg	5 to 30 mg	Once daily	100 to 112		
Oxybutynin patch (Oxytrol)	Transdermal patch: 36 mg	1 patch	Every three to four days	93		
Solifenacin (Vesicare)	Tablet: 5, 10 mg	5 to 10 mg	Once daily	101	Yes	Hepatic (CYP 3A4)/ Renal
Tolterodine (Detrol; Detrol LA)	IR tablet: 1, 2 mg	1 to 2 mg	Twice daily	112 to 115	No	Hepatic (CYP 2D6/ 3A4)
	ER capsule: 2, 4 mg	2 to 4 mg	Once daily	97 to 100		
Trospium (Sanctura)	Tablet: 20 mg	20 mg	Twice daily at least one hour before meals or on an empty stomach	89	No	Renal

ER = extended-release; CYP = cytochrome P450 isoenzymes; IR = immediate-release.

**—Average wholesale cost, based on Red Book, Montvale, N.J.: Medical Economics Data, 2006.*

Information from references 1 through 9.

the interaction between acetylcholine and muscarinic receptors, causes it to contract, and the flow of urine begins. Overactive bladder occurs when the detrusor muscle contracts in the face of submaximal bladder volumes. Anticholinergic drugs suppress such contractions by interfering with the interaction between acetylcholine and muscarinic receptors.

Nonpharmacologic Therapies

Nonpharmacologic intervention is the foundation of treatment for overactive bladder. Pelvic floor muscle training and bladder training have been proven to be effective strategies,[17] and in motivated patients can be more effective than medication.[18] Traditional nonpharmacologic tools and lifestyle modification should be provided consistently as part of a balanced program for improving target symptom control. Reviews of appropriate behavioral methods and pelvic floor training are available.[19]

Older Anticholinergics

Tolterodine and oxybutynin are muscarinic receptor antagonists. Oxybutynin also displays antispasmodic activity in smooth muscle. These agents are recommended for patients with overactive bladder who remain symptomatic despite nonpharmacologic therapy.[20-22] The introduction of extended-release formulations has improved tolerability without substantively impairing the effectiveness of these drugs.[23-27] Completion rates in long-term studies approach 70 percent with extended-release tolterodine, but are as low as 18 percent with immediate-release oxybutynin.[28-30] On average, anticholinergic therapy reduces weekly urge-incontinence episodes by 70 percent. Dry mouth is the most common adverse event, affecting 20 to 30 percent of patients administered these agents.[28-30]

A Cochrane review of randomized controlled trials comparing anticholinergic drugs with placebo or no treatment in patients with overactive bladder showed that patients treated with anticholinergics were more likely to report cure or improvement in their symptoms than those receiving placebo (60 versus 45 percent; $P < .05$, number needed to treat = 7).[31] Maximal cystometric capacity increased 54 mL in patients receiving anticholinergics compared with those receiving placebo. Dry mouth was reported significantly more often in the active medication group (32 versus 14 percent; $P < .05$, number needed to harm = 5); however, similar numbers of patients withdrew because of adverse events. Drug therapy resulted in approximately one less episode of leakage and one less void per 48 hours compared with placebo. Because the placebo-adjusted effectiveness of these agents is marginal, the clinical impact must be weighed against the risk of adverse events.

Newer Agents

Head-to-head studies comparing the three newer agents—trospium, solifenacin, and darifenacin—with immediate-release oxybutynin and tolterodine have suggested similar effectiveness across the class.[10-14,16] Although the attributes of these newer agents in theory could improve tolerability, clinical trials comparing relevant agents to validate this are lacking *(Table 2)*.[10-16]

TROSPIUM

Trospium, a nonselective anticholinergic agent with antispasmodic properties, is approved for the treatment of overactive bladder with symptoms of urge urinary

Comments
Dose should be decreased in patients with moderate hepatic impairment; not recommended for use in patients with severe hepatic impairment.
No formal recommendations exist for dosing in patients with hepatic impairment, but extensive hepatic elimination warrants caution in this setting.
Dose should be decreased in patients with moderate hepatic or severe renal impairment; not recommended for use in patients with severe hepatic impairment. Approximately 15 percent is eliminated unchanged in the urine.
Lowest dose should be used in patients with severe hepatic or renal impairment who are taking CYP 3A4 inhibitors. Tolterodine has a lesser effect at the salivary gland than oxybutynin.
May have functional selectivity Administer once daily in patients with severe renal impairment.

TABLE 2
Key Clinical Trials of Newer Antimuscarinic Agents for Treatment of Overactive Bladder

Study	*Agent(s)*	*Design (no. of participants)*	*Outcomes*
Placebo-controlled studies			
Chapple, et al., 2005[10]	Darifenacin (Enablex) 7.5 to 15 mg per day versus placebo	Pooled analysis of three RCTs (1,059)	Decrease in incontinence episodes per day: –1.25 (7.5 mg), –1.5 (15 mg) versus –0.99 placebo ($P < .004$) Decreases in frequency and severity of urgency, leakage, voids per day, and nocturnal awakenings
Cardozo, et al., 2004[11]	Solifenacin (Vesicare) 5 to 10 mg per day versus placebo	RCT (911)	Decrease in incontinence episodes per day: –1.63 (5 mg), –1.57 (10 mg) versus –1.25 placebo ($P = .002$) Decreases in voids per day, urgency episodes, and nocturia; increase in bladder capacity
Zinner, et al., 2004[12]	Trospium (Sanctura) 40 mg per day versus placebo	RCT (523)	Decrease in incontinence episodes per day: –2.0 versus –1.3 placebo ($P < .001$) Complete dryness in 21% versus 11% placebo Decreases in frequency and severity of urgency, leakage, voids per day, and nocturnal awakenings
Active-comparator studies			
Zinner, et al., 2005[13]	Darifenacin 15 to 30 mg per day versus oxybutynin IR (Ditropan) 5 mg per day or placebo	RCT crossover (76)	Incontinence episodes per week: 10.9 (15 mg), 8.8 (30 mg) versus 9.5 oxybutynin, 14.6 placebo ($P < .05$)
Chapple, et al., 2004[14]	Solifenacin 5 to 10 mg per day versus tolterodine IR (Detrol) 2 mg per day or placebo	RCT (1,081)	Decrease in incontinence episodes per day: –1.42 (5 mg), –1.45 (10 mg) versus –1.14 tolterodine, –0.76 placebo Decreases in voids per day and urgency episodes; increase in bladder capacity
Chapple, et al., 2005[15]	Solifenacin 5 to 10 mg per day versus tolterodine ER (Detrol LA) 4 mg per day	RCT (1,177)	Decrease in incontinence episodes per day: –1.60 (10 mg) versus –1.11 tolterodine ($P < .0001$) Significant decrease in urgency episodes with solifenacin ($P < .05$)
Halaska, et al., 2003[16]	Trospium 40 mg per day versus oxybutynin IR 10 mg per day	RCT (358); unblinded	Similar changes in urodynamic parameters

NOTE: *Differences were not statistically significant or were not tested for significance unless otherwise noted.*

RCT = randomized controlled trial; IR = immediate-release; ER = extended-release.

Information from references 10 through 16.

Adverse effects
Dry mouth: 20.2 to 35.3% versus 8.2% placebo ($P < .05$) Constipation: 14.8 to 21.3% versus 6.2% placebo ($P < .05$) Dyspepsia: 2.7 to 8.4% versus 2.6% placebo ($P < .05$)
Dry mouth: 7.7% (5 mg), 23.1% (10 mg), 2.3% placebo Constipation: 3.7% (5 mg), 9.1% (10 mg), 2.0% placebo Blurred vision: 4.0% (5 mg), 5.9% (10 mg), 2.3% placebo
Dry mouth: 21.8% versus 6.5% placebo ($P < .05$) Constipation: 9.5% versus 3.8% placebo ($P < .05$) Abdominal pain: 3.1% versus 1.1% placebo
Dry mouth: 13.1% (15 mg), 34.4% (30 mg) versus 36.1% oxybutynin, 4.9% placebo Constipation: 9.8% (15 mg), 21.3% (30 mg) versus 8.2% oxybutynin, 3.3% placebo
Early discontinuation: 10.0% (5 mg), 7.1% (10 mg) versus 9.9% tolterodine, 12.0% placebo Dry mouth: 14.0% (5 mg), 21.3% (10 mg) versus 18.6% tolterodine, 4.9% placebo Constipation: 7.2% (5 mg), 7.8% (10 mg) versus 2.6% tolterodine, 1.9% placebo Blurred vision: 3.6% (5 mg), 5.6% (10 mg) versus 1.5% tolterodine, 2.6% placebo
Early discontinuation: 3.5% versus 3.0% tolterodine Dry mouth: 30.0% versus 24.0% tolterodine Constipation: 6.4% versus 2.5% tolterodine Blurred vision: 0.7% versus 1.7% tolterodine
Early discontinuation (< 52 weeks): 25.0% versus 26.7% oxybutynin Dry mouth: 33.0% versus 50.0% oxybutynin Constipation: 7.0% versus 4.0% oxybutynin

incontinence, urgency, or frequency. It has been in use in Europe for more than 20 years. Unlike other anticholinergics, trospium is water soluble and crosses the blood-brain barrier poorly.[9] Although it has been suggested that this feature might minimize centrally mediated events such as drowsiness, nervousness, dizziness, and cognitive impairment, the limited clinical trial data do not support this.

In a prospective, randomized, controlled trial comparing trospium with immediate-release oxybutynin in patients with detrusor instability, there were fewer overall adverse events with trospium (mainly because of a lower incidence of dry mouth).[16] However, there was no difference in CNS adverse effects. Another study evaluated the impact of trospium on somnolence and daytime sleepiness. Trospium did not increase sleepiness or produce other CNS adverse effects; however, the lack of an active comparator arm hinders interpretation of this study.[32]

In one placebo-controlled study that enrolled patients experiencing approximately 30 episodes of urinary incontinence per week, trospium significantly reduced the number of voids and episodes of urge urinary incontinence compared with placebo *(Table 2[10-16])*.[12] After 12 weeks, patients treated with trospium experienced between 1.5 and 4.0 fewer incontinence episodes per week than those treated with placebo and had a greater improvement in quality of life. However, these modest results were tempered by an increased incidence of anticholinergic adverse events. In addition, patients enrolled in this study were highly symptomatic, and thus a favorable effect on quality of life is not surprising.[12] Whether these results can be extrapolated to other populations is debatable.

Trospium was compared with immediate-release oxybutynin in several randomized, double-blind clinical trials.[16,33,34] These studies reported similar improvements in detrusor contractions, maximal cystometric bladder capacity, and bladder volume at first sensation with both agents. However, trospium was better tolerated because of fewer reports of dry mouth.

Collectively, these data suggest that trospium effectively reduces symptoms of overactive bladder and is better tolerated than immediate-release oxybutynin.[16,33,34] Trospium has not been compared with extended-release forms of oxybutynin or tolterodine.

SOLIFENACIN

Solifenacin is a selective M_3 muscarinic receptor antagonist approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, or frequency. Selectivity for the M_3 receptor may confer

TABLE 3
Factors Affecting Selection of Anticholinergic Agents for Treatment of Overactive Bladder

Factor	*Agent to consider*	*Comments*	*References*
Anticholinergic adverse effects	Darifenacin (Enablex), solifenacin (Vesicare), tolterodine ER (Detrol LA), oxybutynin ER (Ditropan XL)	ER products and drugs with uroselectivity may offer enhanced tolerability.	15, 27, 31
CNS adverse effects	Trospium (Sanctura)	Trospium may be less likely to cross the blood-brain barrier (unproven benefit).	31
Cost	Oxybutynin IR	ER and newer agents may be more expensive; generics are available for oxybutynin IR.	22
Drug-drug interactions	Trospium	Agents other than trospium are metabolized by CYP 3A4 or 2D6, which are responsible for elimination of hepatically metabolized drugs.*	9
Effectiveness	Oxybutynin	Nonselectivity may offer more complete suppression of detrusor overactivity. Head-to-head studies of tolterodine and oxybutynin have suggested improved efficacy with oxybutynin.	27
Pregnancy	Oxybutynin	Oxybutynin is pregnancy risk category B whereas all other agents are class C.	2
Severe hepatic impairment	Trospium	Trospium is eliminated renally whereas all other agents undergo extensive hepatic metabolism.*	5, 16, 22, 35
Severe renal impairment	Oxybutynin, tolterodine, darifenacin, solifenacin	Avoid trospium because it is eliminated renally.	9

ER = extended-release; CNS = central nervous system; IR = immediate-release; CYP = cytochrome P450 isoenzyme.

**—The overall correlation between hepatic function and drug disposition is poor.*

Information from references 2, 5, 9, 15, 16, 22, 27, 31, and 35.

improved tolerability given the preferential location of this receptor subtype on the detrusor wall. However, M_3 receptors also are present on smooth muscles in the gastrointestinal tract, salivary glands, eyes, and brain. For this reason, common adverse effects include constipation, dry mouth, blurred vision, fatigue, and cognitive impairment.[5]

Results from several 12-week, double-blind, placebo-controlled studies involving patients with approximately 20 urinary incontinence episodes per week showed that solifenacin reduced urinary frequency by approximately two voids per day compared with a decrease of approximately one void per day with placebo *(Table 2[10-16])*.[5,11,35] Solifenacin also significantly improved urgency, nocturia, and bladder emptying. Compared with immediate-release tolterodine, solifenacin resulted in greater decreases in urgency and incontinence episodes but produced anticholinergic side effects at a similar frequency.[14,36] One possible explanation for these findings is that trials of solifenacin used doses up to the maximum of 10 mg, whereas the dose of tolterodine was capped at 2 mg. Solifenacin improved health-related quality of life in patients with overactive bladder and urinary incontinence.[36]

Another study compared 5 to 10 mg of solifenacin daily with 4 mg of extended-release tolterodine daily.[15] In this study, patients treated with solifenacin had better symptom control but experienced more adverse events. Again, however, the dosing strategy may explain these findings: patients treated with solifenacin initially were given 5 mg daily and could request an increase in dosage after four weeks; 48 percent of patients requested such increase and subsequently were treated with 10 mg daily. In the tolterodine arm, 51 percent of patients requested a dosage increase, but they already were receiving the maximal dosage.

DARIFENACIN

Similar to solifenacin, darifenacin is a muscarinic receptor antagonist with enhanced specificity for the M_3 receptor subtype. It is approved for the management of overactive bladder, and improves overactive bladder symptomatology to an extent similar to that of other agents *(Table 2)*.[10-16] One unique parameter that has been examined with darifenacin is "warning time": the time from the first sensation of urgency to the time of

voluntary urination or incontinence.[37] An increase in this duration may permit more patients to experience or maintain continence. Darifenacin increased warning time by 4.3 minutes compared with placebo ($P = .003$), and 47 percent of patients treated with darifenacin experienced a 30 percent or greater increase in mean warning time compared with only 20 percent of patients treated with placebo ($P = .009$).[37]

In a crossover study with immediate-release oxybutynin, the incidence of dry mouth was significantly lower with darifenacin 15 mg than with oxybutynin (13 versus 36 percent, respectively; $P < .05$) but not with darifenacin 30 mg (34 versus 36 percent).[13] Constipation was more common in patients given darifenacin 30 mg (21 versus 8 percent with oxybutynin; $P < .05$) but not in those given 15 mg (10 percent). Effectiveness was similar for patients receiving either dose of darifenacin and those receiving oxybutynin. Comparisons of darifenacin with extended-release oxybutynin or tolterodine are lacking.

Selecting Pharmacologic Agents for Overactive Bladder

The availability of three newer anticholinergic drugs increases the pharmacologic armamentarium for the treatment of overactive bladder. Caution is required with each of these agents, particularly in patients with contraindications to anticholinergic therapy (e.g., untreated open-angle glaucoma, constipation, urinary retention, gastrointestinal disease). A careful evaluation of the balance between benefits and harms, with special attention paid to quality of life, is warranted when considering use of these agents. Appropriately conducted trials are needed to determine the clinical value of functional, structural, and pharmacokinetic nuances. The pharmacokinetic differences among anticholinegic agents allow for the selection of agents based on individual factors *(Table 3)*.[2,5,9,15,16,22,27,31,35] In the absence of definitive comparative data, a reasonable strategy is to select a therapy according to the individual patient and to try alternative agents if the first is not effective or cannot be tolerated.

Members of various family medicine departments develop articles for "Clinical Pharmacology." This is one in a series coordinated by Allen F. Shaughnessy, Pharm.D., and Andrea E. Gordon, M.D., Tufts University Family Medicine Residency, Malden, Mass.

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Contractile responses to α_1-adrenoceptor agonists in isolated human male and female urethra

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Objective To investigate the contractile responses mediated through α_1-adrenoceptors in human urethra and to evaluate the effectiveness of NS-49 [(R)-(–)-3′-(2-amino-1-hydroxyethyl)-4′-fluoromethanesulphonanilide hydrochloride], a novel α_1-adrenoceptor agonist, against contraction of the human urethra.

Materials and methods The contractile responses were assessed in 10 male prostatic urethrae and six female urethrae. Antagonism was evaluated in the urethra using phenylephrine, a nonselective α_1-adrenoceptor agonist, cumulatively applied > 20 min after applying 0.1 μmol/L prazosin or 0.1 μmol/L 5-methylurapidil, a selective α_{1A}-adrenoceptor antagonist. Agonism was determined in both male and female urethrae to obtain the concentration-response curve for the agonist.

Results Phenylephrine caused both male and female urethrae to contract, and showed high potency and efficacy. Prazosin antagonized these contractions with low affinity (apparent pK_B of 8.30 in male urethrae). 5-Methylurapidil, also antagonized the contractions with low affinity (apparent pK_B of 7.88 in male urethrae). Noradrenaline and phenylephrine caused both male and female urethrae to contract, with high potency and efficacy. A novel and selective α_{1A}-and α_{1L}-adrenoceptor agonist, NS-49, induced contractile responses with high potency and moderate efficacy, whereas methoxamine induced contractions with low potency and moderate efficacy. Norephedrine was a very weak contractile agonist.

Conclusion In the human urethra, phenylephrine-induced contractions were mediated through α_{1L}-adrenoceptors and not through α_{1A}-adrenoceptors. Contractions of the human urethra induced by NS-49 were also mediated mainly through α_{1L}-adrenoceptors, with high potency and moderate efficacy. NS-49 may therefore be useful for the treatment of urinary stress incontinence, with minimal side-effects because it has subtype selectivity.

Keywords α_1-adrenoceptor, contractions, human urethra, NS-49

Introduction

Native and cloned α_1-adrenoceptors have recently been classified into three subtypes, α_{1A}, α_{1B}, and α_{1D}, on the basis of their pharmacological, structural and signal-transduction properties [1,2]. In addition to these three receptor subtypes, another subtype, α_{1L}, was proposed from functional pharmacological studies, although its existence has not yet been verified at the molecular level [3]. The α_{1L}-adrenoceptor shows low affinity for prazosin ($pA_2 < 9$), whereas α_{1A}-, α_{1B}- and α_{1D}-adrenoceptors show high affinity for prazosin ($pA_2 > 9$).

The lower urinary tract, including the bladder base, the proximal urethra and the prostate, contracts upon stimulation with noradrenaline, and α_1-adrenoceptor stimulation through α_1-adrenoceptors on lower urinary tract smooth muscle cells is considered to play an important role in maintaining urinary continence [4]. As binding and molecular biological studies have indicated that the α_{1A}-adrenoceptor subtype and α_{1a}-adrenoceptor mRNA are predominant in the human lower urinary tract [5–9], this receptor subtype is thought to mediate contractile responses to noradrenaline [10–12]. However, functional pharmacological studies by Ford *et al.* [13] revealed that it is α_{1L}-adrenoceptor that is mainly involved in noradrenaline-induced contractions in the human lower urinary tract. In addition, binding studies by Taniguchi *et al.* [14] suggested the possible existence of α_{1L}-adrenoceptor in addition to α_{1A}-adrenoceptor subtypes in the human prostatic urethra. Therefore, a selective α_{1L}-adrenoceptor antagonist rather than a selective α_{1A}-adrenoceptor antagonist may be useful in the treatment of urinary difficulty caused by prostatic hypertrophy [15]. Furthermore, an α_{1L}-

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adrenoceptor agonist may also be useful in the treatment of urinary stress incontinence.

NS-49 [(R)-(−)-3′-(2-amino-1-hydroxyethyl)-4′-fluoro-methanesulphonanilide hydrochloride], is a novel α_1-adrenoceptor agonist that shows selective α_{1A}-adrenoceptor agonistic activity in Chinese hamster ovary (CHO) cells expressing the cloned human α_{1A}-, α_{1B}-, or α_{1D}-adrenoceptor subtypes [16] and, in functional studies, both α_{1A}-and α_{1L}-adrenoceptor agonistic activities [17]. This compound is now being developed by the Nippon Shinyaku Company as a therapeutic agent for urinary stress incontinence, especially for female patients, and it is expected to be superior to nonselective α-adrenoceptor agonists in both efficacy and safety [18]. However, there have been few functional studies on the human female urethra.

In the present study, we used urethrae isolated from both male and female patients to examine contractile responses mediated through α_1-adrenoceptors. To determine the α_1-adrenoceptor subtypes involved in the contractile responses, we first investigated the antagonistic potencies of prazosin and a selective α_{1A}-adrenoceptor antagonist, 5-methylurapidil [19] against phenylephrine-induced contractions in the urethra. We then assessed the ability of NS-49 to cause contraction in both male and female urethrae and compared it with the activities of noradrenaline and phenylephrine (nonselective α-adrenoceptor agonists), and methoxamine (a relatively selective α_{1A}-adrenoceptor agonist), and norephedrine (a sympathomimetic amine), the last two of which are in clinical use for the treatment of urinary stress incontinence.

Materials and methods

All experiments were carried out with the approval of the research ethical committee of the Faculty of Medicine, The University of Tokyo. For all patients, fully informed consent was obtained after explaining the study and before surgery.

NS-49 was synthesized by Nippon Shinyaku (Kyoto, Japan). The following drugs were obtained from commercial sources: *l*-noradrenaline bitartrate, *l*-phenylephrine hydrochloride, methoxamine hydrochloride, prazosin hydrochloride and desmethylimipramine hydrochloride (Sigma, St. Louis, MO); dl-norephedrine hydrochloride (Tokyo Kasei, Tokyo, Japan); 5-methylurapidil (Research Biochemicals, Natik, MA); and deoxycorticosterone acetate and propranolol hydrochloride (Nacalai Tesque, Kyoto, Japan). Deoxycorticosterone (10 mmol/L) was dissolved in ethanol, then diluted with distilled water; other drugs were dissolved in distilled water.

Fresh prostatic urethra was obtained at retropubic prostatectomy or total cystourethrectomy from 10 men (mean age 64.7 years, SEM 2.6) with BPH or bladder cancer. The proximal urethra was obtained at total cystourethrectomy from six women (mean age 51.6 years, SEM 3.6) with bladder cancer. The patients had had no treatment with α_1-adrenoceptor antagonists for BPH or hypertension for at least one week before surgery. Specimens were kept in cold Krebs' solution and the contraction assessed within 24 h.

Urethral specimens were cut into segments, the mucosal layer removed and transverse strips of 10 mm long and about 2 × 2 mm in cross-sectional area were cut. For a contraction experiment, a strip was mounted in an organ bath containing 10 mL of Krebs' solution (composition in mmol/L; 120.5 NaCl, 5.9 KCl, 2.5 $CaCl_2$, 1.2 $MgCl_2$, 1.2 NaH_2PO_4, 15.5 $NaHCO_3$ and 11.5 glucose, pH 7.5) gassed with a mixture of 95% O_2 and 5% CO_2, maintained at 37 °C. The strip was stretched to a resting tension of 1 g and equilibrated for 60 min, during which it was washed with Krebs' solution at 15-min intervals. Changes in tension were isometrically detected with a force-displacement transducer (T7–30–240, Toyo Baldwin, Tokyo) connected to an amplifier (AP-620G, Nihon Kohden, Tokyo) and a polygraph recorder (RJG-4024, Nihon Kohden).

The concentration-response curve (CRC) generated by the cumulative application of phenylephrine (0.01–3000 μmol/L) was obtained and the strip was then washed several times at 15-min intervals until the tension had returned to the basal level. This procedure, which took 90 min, was repeated until a reproducible CRC for phenylephrine was obtained; only such strips were used for the subsequent study, with the last CRC regarded as the control response. In antagonism studies, phenylephrine was then applied cumulatively > 20 min after the application of 0.1 μmol/L prazosin or 0.1 μmol/L 5-methylurapidil. In agonism studies, the agonist was then applied cumulatively to obtain a CRC for the agonist. The CRC for noradrenaline was obtained in the presence of 0.1 μmol/L desmethylimipramine and 5 μmol/L deoxycorticosterone to inhibit neuronal and non-neuronal noradrenaline uptake. The reproducibility of the control response to phenylephrine was confirmed in another strip from the same patient (Fig. 1). In each experiment, an agonist was applied until the maximal contractile response was obtained. Propranolol (1 μmol/L) was present in the Krebs' solution throughout the experiment to prevent α-adrenoceptor-mediated responses.

The contractile activity of each agonist was evaluated as its potency and its efficacy. The maximal efficacy (E_{max}) was expressed as a percentage of the maximal contraction induced by phenylephrine. The potency was expressed as the EC_{50} value, the concentration of agonist that produced half the maximal contraction. EC_{50} values

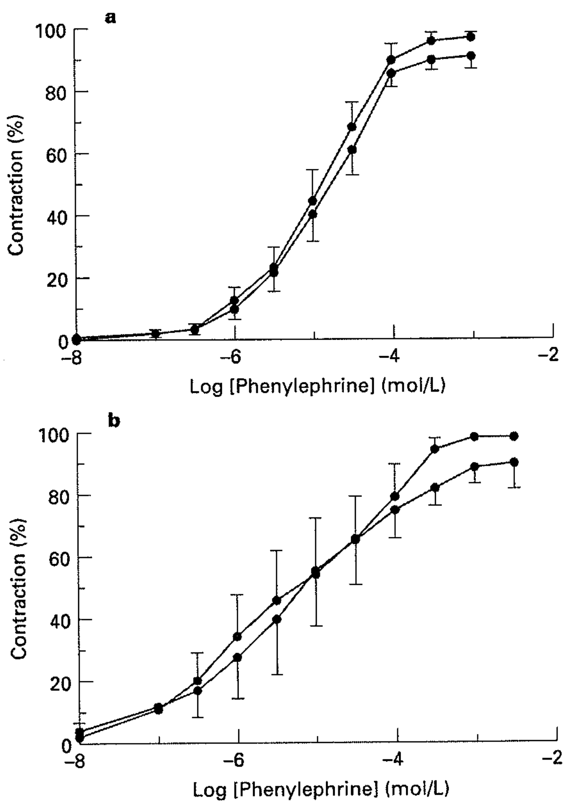

Fig. 1. The reproducibility of the concentration-response curves for phenylephrine (green, first response; red, second response) in isolated **a**, male prostatic and **b**, female proximal urethra. Each value represents the mean (SEM) of 10 experiments in **a** and four in **b**.

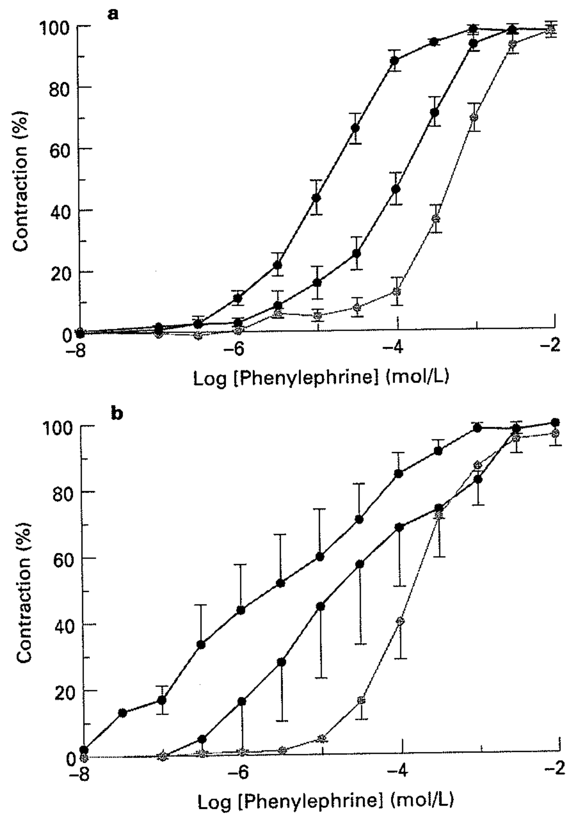

Fig. 2. Antagonistic effects of prazosin (light green) and 5-methylurapidil (red), compared with the control (green), on phenylephrine-induced contractions in isolated **a**, male prostatic urethra and **b**, female proximal urethra. Each value is the mean (SEM) of 4–7 experiments.

were calculated from linear regression of log $[E/(E_{max} - E)]$ on the logarithm of the concentration, where E is the response to a given concentration, and data were expressed as pEC_{50}, the negative logarithm of EC_{50}. Antagonist activities were expressed as apparent pK_B values calculated as $-\log [I/(CR-1)]$ [20], where CR is the concentration ratio, i.e. the ratio of the EC_{50} with no antagonist to that with an antagonist, and I is the molar concentration of the antagonist. The results were expressed as the mean (SEM).

Results

Phenylephrine induced concentration-dependent contractions in male urethral strips. The effects of prazosin and 5-methylurapidil on these contractions in strips from both sexes are shown in Fig. 2. Prazosin (0.1 μmol/L) and 5-methylurapidil (0.1 μmol/L) antagonized phenylephrine-induced contractile responses competitively in the male urethra. The apparent pK_B values for prazosin and 5-methylurapidil were 8.30 (0.24) (four strips) and 7.88 (0.09) (seven strips), respectively. In the strips of female urethra, the CRC to phenylephrine was much flatter than in the male strips. The antagonists shifted the CRC to the right in a similar manner, but in the presence of prazosin the CRC was much steeper.

The contractile responses to α-adrenoceptor agonists in the strips from both sexes are shown in Fig. 3 and the contractile potency (pEC_{50}) and E_{max} for agonists in male and female urethral strips are given in Table 1. In male prostatic urethral strips, phenylephrine induced contractions with moderate potency; the maximum contractile response was 0.204 (0.029) g force per strip ($n=10$). Noradrenaline induced contractions with high potency and high efficacy, NS-49 induced contractions with high potency and moderate efficacy, and methoxamine with moderate efficacy but low potency. The contractile activity of norephedrine was very weak

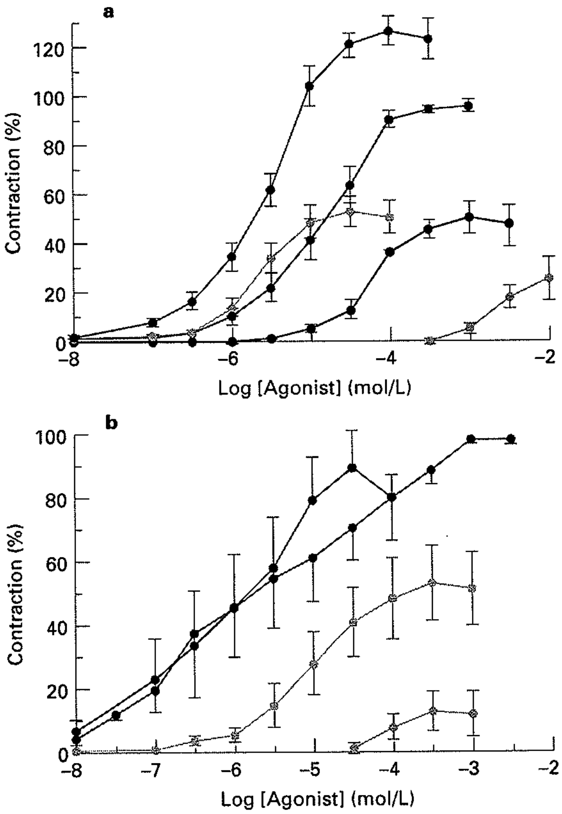

Fig. 3. Contractile activities of α-adrenoceptor agonists (green, phenylephrine; light green, NS-49; red, noradrenaline; light red, norephedrine; black, methoxamine) in **a**, isolated male prostatic urethra and **b**, female proximal urethra. Each value represents the mean (SEM) of 3–10 experiments in **a** and 3–6 experiments in **b**.

compared with the other agonists. In female proximal urethral strips, phenylephrine induced contractions with high potency, inducing maximum contractions of 0.459 (0.130) g force per strip ($n=6$). Noradrenaline also induced contractions with high potency and high efficacy, while NS-49 induced contractions with moderate potency and efficacy. Norephedrine showed almost no contractile activity.

Discussion

The predominant α_1-adrenoceptor subtype in the human prostate is α_{1A} or α_{1a} [5–8,11]. According to the few reports on α_1-adrenoceptors of the human male urethra [10,12], the contraction of the urethra is mediated by the α_{1A}- or α_{1D}-adrenoceptor subtype. Studies on the α_1-adrenoceptors of the human female urethra are rare.

Using a selective α_{1A}-adrenoceptor antagonist, RS-17053, Ford *et al.* [13] showed that it is α_{1L}-adrenoceptor that is mainly involved in noradrenaline-induced contractions in the human male lower urinary tract. In addition, we have previously shown using binding studies that an α_{1L}-adrenoceptor subtype, in addition to the α_{1A}-adrenoceptor subtype, may also be present in human male prostatic urethra [14]. The present study shows that prazosin has low affinity in antagonism to adrenoceptor-mediated contractions of male and female urethra, indicating that these contractions are mediated mainly through an α_{1L}-adrenoceptor subtype; this result is consistent with previous work. In addition, 5-methylurapidil had low affinity in antagonism to phenylephrine-induced contractions in both male and female urethra, indicating that human urethral contraction is not mediated through α_{1A}-adrenoceptors.

The apparently flat CRCs for phenylephrine in the female urethra, in contrast to those in the male, suggest that two classes of α_1-adrenoceptors may be involved in the contraction of the female urethra, whereas the population in the male urethra is more uniform. However, considering the large variations in the responses to phenylephrine, attributable to the difficulty in obtaining uniformly conditioned female urethrae, further studies are needed to evaluate the possible existence of several classes of receptors mediating contraction in the female urethra.

Table 1 Contractile activities of α-adrenoceptor agonists in isolated male prostatic urethra and female proximal urethra

	Male, mean (SEM)			*Female, mean (SEM)*		
Agonists	*n*	*pEC$_{50}$*	*Max efficacy (%)*	*n*	*pEC$_{50}$*	*Max efficacy (%)*
Phenylephrine	10	4.88 (0.15)	100	6	5.58 (0.47)	100
NS-49	4	5.69 (0.10)	52.9 (6.3)	5	5.06 (0.17)	52.4 (9.2)
Noradrenaline	4	5.54 (0.11)	127.2 (5.9)	3	6.13 (0.40)	91.1 (11.7)
Norephedrine	4	<4	25.4 (8.9)	3	<4	12.8 (6.2)
Methoxamine	3	4.32 (0.12)	50.8 (6.8)	-	-	-

NS-49 is a novel α_1-adrenoceptor agonist designed for the treatment of urinary stress incontinence; it showed selective α_{1a}-adrenoceptor agonist activity in CHO cells expressing human cloned α_{1a}-, α_{1b}-, or α_{1d}-adrenoceptors [16], and α_{1A}-and α_{1L}-adrenoceptor agonist activities in contraction studies in various smooth-muscle preparations from experimental animals [17]. We have already shown that NS-49 binds with high affinity to α_1-adrenoceptors in the human male urethra [14]. The drug also produced highly selective contraction of isolated dog urethra over carotid artery. However, the present study is the first to evaluate the agonistic activity of NS-49 in contractile responses in both male and female urethra.

Reportedly, NS-49 had low efficacy ($< 30\%$) in CHO cells expressing cloned human α_{1B}- or α_{1D}-adrenoceptor when agonism was evaluated as the increasing activity of intracellular calcium ion concentration [16]. Moreover, in these cells, NS-49 showed clear antagonistic activities against the response to noradrenaline. On the other hand, NS-49 showed agonistic activity with $> 60\%$ maximal efficacy in cells expressing cloned human α_{1A}-adrenoceptor. We did not evaluate the antagonistic activity of NS-49 in these cells because of the difficulty in evaluating it accurately in a partial agonist which has $\geqslant 50\%$ efficacy, such as NS-49.

In the present study, NS-49 induced contractions of both male and female urethra with high or moderate potency and moderate efficacy compared with those for other α_1-adrenoceptor agonists. These results indicate that NS-49 elicited urethral muscle contractions through α_{1L}-adrenoceptors, thereby implying that NS-49 has not only α_{1A}-agonistic activity, but also α_{1L}-agonistic activity, in human tissues.

In conclusion, these results suggest that NS-49, a selective $\alpha_{1A/1L}$-adrenoceptor agonist, effectively induces contractions in the human urethra and that human urethral contractions are mediated mainly through α_{1L}-adrenoceptors. NS-49 is therefore a promising drug for the treatment of urinary stress incontinence and is expected to have few side-effects because it has subtype selectivity. NS-49 may be especially useful for the treatment of female stress incontinence.

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